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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,009	12/20/2001	Christopher Thomas Brain	4-30972A	1971
1095	7590	03/04/2004	EXAMINER MCKENZIE, THOMAS C	
THOMAS HOXIE NOVARTIS, CORPORATE INTELLECTUAL PROPERTY ONE HEALTH PLAZA 430/2 EAST HANOVER, NJ 07936-1080			ART UNIT 1624	PAPER NUMBER

DATE MAILED: 03/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/009,009

Applicant(s)

BRAIN ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,12-14 and 16-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1,3,4,12-14,16 and 17 is/are allowed.
- 6) ☒ Claim(s) 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date 02/29/2004.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This action is in response to amendments filed on 12/18/03. Applicant has canceled claims 15. Claim 18 is new. There are nine claims pending and 9 under consideration. Claims 1, 3, 4, 12, and 17 are compound claims. Claim 16 is a composition claim. Claim 18 is a use claim. Claims 13 and 14 are synthesis claims. This is the third action on the merits. The application concerns some carbonyl-piperidine and carbonyl-piperazine compounds, compositions, synthesis, and uses thereof.

Response to Amendment

2. Applicants' cancellation of claim 15 and substitution of claim 18, which lists the diseases intended to be treated, overcomes the indefiniteness rejection made in point #3 of the previous office action.

Claim Rejections - 35 USC § 112

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. New claim 18 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain, does not reasonably provide enablement for treating inflammatory diseases, inflammatory disorders, edema, spasms, and septic shock. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to

operability and how to make the claimed process work. The factors to be considered in making an enablement rejection were summarized in the previous office action. The issue is the correlation between the assays used by Applicants and treatment of the rejected diseases.

a) Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating bradykinin related disease is found in the last two paragraphs on page 21, which merely states Applicants' intention to do so. Applicants describe formulations in the first and second paragraphs on page 24. These are prophetic and there is no working example of any formulation required to practice Applicants therapeutic claim. Doses required to practice their invention are described in the fourth paragraph on page 23. A 2,000-fold range of doses is recommended. Since no bradykinin antagonist has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is an *in vitro* bradykinin B₁ binding assay described in pages 19 and 20 with no data.

Applicants do not assert and it not art-recognized this assay is correlated to clinical efficacy for the treatment of all bradykinin related disease. There is an *in vivo* test on the tails of monkeys that is art-recognized as predictive of efficacy for the treatment of pain in humans described in the second and third paragraph on page 21. c) There is no working example of treatment of any disease in man or of any rejected disease in animals. d) The nature of the invention is clinical treatment of disease with bradykinin antagonists, which involves physiological activity. e) Marceau (Pharmacol. Rev.) summarizes the state of the clinical arts in bradykinin related diseases in the last complete sentence on page 19 that, "[p]ractically nothing is known about the clinical pharmacology of the B1R [the bradykinin B₁ receptor]".

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1. The term inflammation is very broad. Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can

take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages that have stuck tightly together, typically to wall something off.

Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as *Salmonella*, *Staphylococcus*, *Streptococcus* (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent.

Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs, corticosteroids, and colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more sinuses. It commonly accompanies upper respiratory viral infections and in most cases requires no treatment.

Pharyngitis (tonsillitis) is an inflammatory illness of the mucous membranes and underlying structures of the throat (nasopharynx, uvula, and soft palate). The illness can be caused by bacteria, viruses, mycoplasmas, fungi, and parasites, and uncertain causes, especially *Streptococcus pyogenes*, adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, and *Mycoplasma pneumoniae*. Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly *Staphylococcus Aureus*). Fungi or viruses can

cause the disease. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye) is inflammation of the conjunctiva and can be caused by many microorganisms, including staphylococci, *Haemophilus influenzae*, streptococci, gonococci, and viruses such as adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.

Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-18 and IL-18, and IFN- .

Pneumonia is an inflammation of the lungs that can be caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), bacteria, fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents.

Other inflammations in the respiratory system include CF, adult respiratory distress syndrome, asthma, and bronchitis.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment

is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is an inflammation of the outer covering of the brain and spinal cord. Virtually any known infectious agent can cause it. Thus, if it were caused by *Haemophilus influenzae* or *Neisseria meningitis*, the antibiotic derivative rifampin would be used.

Encephalitis is an inflammation of the brain itself. It is most often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also takes the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids are an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything that obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia, and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the exterior of the body. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when *Neisseria gonorrhoeae* is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially *Candida albicans*), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis

usually arises following pregnancy. Treatment is usually bed rest with beta-blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder, which is associated with the presence of *Mycobacterium paratuberculosis*. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as *Candida albicans*, dentures, chemotherapy, and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to *Lactobacillus* capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis, and cat-scratch disease. Treatment is thus to the underlying cause. For example, diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the

eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from *Helicobacter pylori*. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee sting), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrown hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. The inflammation of acne is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus *Propionibacterium*

acnes, which populate the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), that are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those, which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

For a compound or genus to be effective against inflammation generally is contrary to medical science. The scope also includes edema, spasms, and septic shock. Thus, the scope of claims is extremely broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants argue that all compounds embraced by claim 1 have bradykinin B₁ receptor antagonist activity. That is not on point and is not the basis of the

rejection. Where is the evidence that all such antagonists treat spasms, say? The evidence supplied by Marceau (Pharmacol. Rev.) says they cannot.

Allowable Subject Matter

4. Claims 1, 3, 4, 12-14, 16, and 17 are allowed.

Conclusion

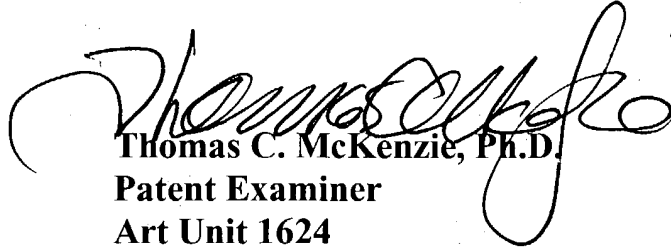
5. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

6. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts

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to reach the Examiner by telephone are unsuccessful, please contact James O.
Wilson, Acting-SPE of 1624 at (571)-272-0661.



Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK